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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 11/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/623,543	BRIDON ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22,24,25,28,33-36,38,41-43,45 and 48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *33* is/are allowed.

6)☒ Claim(s) *22,24,25,28,34-36,38,41-43,45 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The examiner of the application has changed. This case has now been transferred as of ***10/24/2005***. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Brandon Fetterolf, Group Art Unit 1642.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 02/17/2005 has been entered.

Claims 22, 24-25, 28, 33-36, 38, 41-43, 45 and 48 are currently pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Rejections Withdrawn:

The rejection of claims 22, 24-25, 28, 33-36, 38, 41-43, 45 and 48 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement has been withdrawn in view of Applicants amendments.

The rejection of claims 22, 24-25 and 35-36, 38, 41-43, 45 and 48 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been withdrawn in view of Applicants amendments.

The rejection of claim 33 under 35 U.S.C. 102 (e) as being anticipated by U.S. Patent number 5,981,484 has been withdrawn in view of Applicants Remarks.

New Rejections necessitated by amendment and reconsideration:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 34 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. THIS IS A NEW MATTER REJECTION.

Claim 34 recites a method of using a modified kringle 5 peptide wherein said kingle 5 peptide comprises SEQ ID NO: 8 and a maleimido group coupled to said kingle 5 peptide wherein said maleimido group reacts with a thiol group on a blood protein to form a covalent bond, for the manufacturing an anti-angiogeneic medicament having an extended in vivo half-life compared to said kringle 5 peptide in the absence of said maleimido group. However, a review of the specification and claims, as originally filed, does not appear to support the limitation " in the absence of said maleimido group". Moreover, Applicants have not provided any information as to where this limitation can be found. As such, Applicant is invited to point to clear support or specific examples of the claimed limitation in the specification as-filed or remove such amendatory language in response to this office action.

Claims 35-36, 38, 41, 42-43, 45 and 48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a conjugate of formula: blood component-reactive group-peptide, wherein said peptide is kringle 5 peptide comprising SEQ ID NO: 8, reactive group is maleimido group bonded to a thiol group of a blood component by means of a stable

covalent bond, does not reasonably provide enablement for a conjugate of formula: blood component-reactive group-peptide, wherein said peptide is kringle 5 peptide comprising SEQ ID NO: 8, reactive group is a succinimidyl group bonded to an amino group, a hydroxyl group or a thiol group of a blood component by means of a stable covalent bond. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The instant claims read on a conjugate of formula: blood component-reactive group-peptide, wherein said peptide is kringle 5 peptide comprising SEQ ID NO: 8, reactive group is either a succinimidyl or maleimido group bonded to an amino group, a hydroxyl group or a thiol group of a blood component by means of a stable covalent bond. Thus, the claims read a conjugate wherein the blood component is linked to either a succinimidyl or a maleimido group which is linked to peptide comprising the amino acid sequence of SEQ ID NO: 8.

The scope of the instant claims is not commensurate with the enablement of the instant disclosure, because practice of the claimed invention would require undue experimentation by an artisan of ordinary skill in the art. The instant specification is not enabling for claims drawn to a conjugate of formula: blood component-reactive group-peptide, wherein said peptide is a kringle 5 peptide comprising SEQ ID NO: 8, reactive group is a succinimidyl group bonded to an amino

group, a hydroxyl group or a thiol group of a blood component by means of a stable covalent bond. The specification teaches (page 10, lines 27 to page 11, line 3) that to form covalent bonds with a functional group on a protein, one may use as a chemical reactive group with a wide variety of active carboxyl groups such as N-hydroxysuccinimide (NHS), N-hydroxy-sulfosuccinimide (Sulfo-NHS), maleimide-benzoyl-succinimide (MBS), gamma-maleimido-butyryloxy succinimide ester (GMBS) and maleimidopropeionic acid (MPA). With regards to the maleimido groups, the specification provides (page 12, line 3) the formation of a conjugate wherein a free thiol is linked to a maleimido reactive group which is further linked to an R group. With regards to the succinimidyl groups, ie., succinimide or NHS esters, the specification discloses (page 11, lines 5-20) that primary amines are the principal targets for NHS ester, wherein an amide bond is formed when the NHS ester conjugate reacts with a primary amine releasing N-hydroxysuccinimide. Thus, in view of the specification, a reaction between a kringle 5 peptide comprising an amino acid sequence of SEQ ID NO: 8 modified with a succinimidyl group and a blood protein does not appear to result in the conjugate as presently claimed.

Moreover, those of skill in the art recognize that a reaction between a peptide modified with an activated ester and a primary amine would result in the displacement of the activated ester and the formation a covalent bond between the peptide and primary amine. For example, Bailey P. D. (An Introduction to Peptide Chemistry, New York, Wiley & Sons, 1990) discloses the advantages of using activated esters as compared to methyl esters for coupling reactions (Section 3.3, page 132). Specifically, Bailey teaches that the formation of an activated ester results in a stabilized –OR group with leaves upon reaction with a primary amine (see reaction scheme, page 132, Section 3.3). Moreover, Pietersz (Bioconjugate Chemistry 1990; 1: 89-94) reviews the linkages between cytotoxic drugs and monoclonal antibodies. In particular, Pietersz provides activated esters formed between N-hydroxysuccinimide and a carboxylic acid of a drug, wherein the reaction of the active ester with an amino group of an antibody displaces the succinimidyl group giving rise to a stable amide linkage between the drug and antibody (*See* Scheme II). Thus, in view of the teachings above, and the lack of guidance and or exemplification in the specification, it would not be predictable that the method would function as contemplated. Thus, it would require undue experimentation by one of skill in the art to practice the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 22 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Davidson et al. (WO 97/41824, 13 November 1997/ IDS reference AM on sheet 1 of 3, February 2001) of record.

Davidson et al. disclose (see page 43, Example 5, line 12 and attached database sheet) a kringle 5 peptide or ester thereof having an amino aid sequence which appears to be 100% identical to the currently claimed modified peptide comprising SEQ ID NO: 8. With regards to the ester, the WO application teaches that the peptide may be modified to include an activated ester derivative, wherein the activated ester derivative includes, but is not limited, to N-hydroxysuccinimide derived esters (page 12, lines 20-26). Davidson et al. further teach (page 19, line 28 to page 25, line 16) that the kringle 5 peptide, as well as derivatives and analogs thereof are comprised in a composition and administered for the treatment of both primary and metastatic solid tumors and compounds of several organ systems. The WO document also discloses methods of manufacturing the anticipated composition including a kringle 5 peptide and derivatives and analogs thereof, see page 13, line 1-page 15, line 36 and page 43, Example 5. Thus, while Davidson et al. does not explicitly teach that the modified kringle 5 peptide having a N-hydroxysuccinimide derived activated ester reacts with an amino group or a hydroxyl group on a blood component to form a stable covalent bond, the claimed functional limitation would be an inherent property of the referenced method since the specification discusses (page 11, lines 5-20) that primary amines are the principal targets of NHS esters, wherein accessible α-amine esters present on the N-termini of proteins react with NHS

esters. Thus, it does not appear that the claim language or limitation results in a manipulative difference in the method steps when compared to the active steps of the prior arts disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

Moreover, even though the claims are drawn to a mechanism by which the reactive group reacts with an amino group of a blood component, the claimed method does not appear to distinguish over the prior art teaching of the same or nearly the same method. The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 22, 24-25, 35-36, 38, 41-43, 45 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davidson et al. (WO 97/41824, 13 November 1997/ IDS reference AM on sheet 1 of 3, February 2001) in combination with Peeters et al. (J. Immunol Methods 1989; 120: 133-143) in view of Humphries et al. (J. Tissue Culture Methods 1994; 16: 239-242).

Davidson et al. disclose, as discussed above for claims 22 and 24, a kringle 5 peptide or ester thereof having an amino aid sequence which appears to be 100% identical to the currently claimed modified peptide comprising SEQ ID NO: 8, wherein the peptide may be modified to include an activated ester derivative such as N-hydroxysuccinimide derived esters (page 12, lines 20-26). Davidson et al. further teach (page 19, line 28 to page 25, line 16) that the kringle 5 peptide, as well as derivatives and analogs thereof are comprised in a composition and administered for the

treatment of both primary and metastatic solid tumors and compounds of several organ systems. The WO document also discloses (page 13, line 1-page 15, line 36 and page 43, Example 5) methods of manufacturing the anticipated composition including a kringle 5 peptide and derivatives and analogs thereof. Moreover, Davidson et al. teach coupling the kringle 5 protein with carrier proteins to form a conjugate (page 35, lines 22-30). For example, the WO document teaches using glutaraldehyde to link kringle 5 peptide fragments containing a lysine residue with bovine serum albumin (page 36, lines 8-9).

Davidson et al. does not explicitly disclose that the reactive group, i.e. activated ester, is a maleimido group, wherein the reactive group is reactive with a thiol group on a blood protein such as serum albumin. Nor does Davidson et al. teach a conjugate comprising the formula: blood component-reactive group-peptide, wherein the peptide is a kringle 5 peptide comprising SEQ ID NO: 8, the reactive group is a maleimido group which is covalently bonded to a thiol group of the blood component.

Peeters et al. discloses comparison of four bifunctional reagents for coupling peptides to proteins and the effect of the three moieties on the immunogenicity of the conjugates (Title). Specifically, the reference teaches that the bifunctional reagent, MHS (succinimidyl 6-(N-maleimido)-n-hexanoate) is the bifunctional reagent of choice for coupling peptides to proteins because of it lower potential for immunogenicity, greater flexibility and greater stability in aqueous solution (page 142, 2nd column, 1st paragraph). Peeters et al. further teach the synthesis (page 134, Figure 1) of protein-peptide conjugates, wherein the protein is linked to the bifunctional reagent which is further linked to the peptide via a thiol group.

Humphries et al. teach that carrier proteins include, but are not limited to bovine serum albumin (Page 239, 2nd column, C. Chemicals).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use MHS instead of glutaraldehyde to link a carrier protein, such as bovine serum albumin, with a kringle 5 peptide in view of the teachings of Peeters et al.. One would have been motivated to do so because as taught by Peeteres et al, MHS is the bifunctional reagent of choice for coupling peptides to proteins because of its low potential for immunogenicity, greater flexibility and greater stability in aqueous solution. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by using MHS instead of glutaraldehyde as taught by

Peeters et al. to link a carrier protein, such as bovine serum albumin, with a kringle 5 peptide, one would achieve a peptide-linked to a carrier protein which upon administration is less immunogenic, more state and more flexible.

Claims 28 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davidson et al. (WO 97/41824, 13 November 1997/ IDS reference AM on sheet 1 of 3, February 2001) in combination with Peeters et al. (J. Immunol Methods 1989; 120: 133-143) in view of Yeh et al. (J. Tissue Culture Methods 1994; 16: 239-242).

The combination of Davidson et al. and Peeters et al. disclose, as described above for claims 22, 24-25, 35-36, 38, 41-43, 45 and 48, a peptide conjugate, wherein the peptide conjugate comprises a kringle 5 peptide linked via a maleimido group to a carrier protein such as bovine serum albumin. The reference further teaches that the kringle 5 peptide, as well as derivatives and analogs thereof are comprised in a composition and administered for the treatment of both primary and metastatic solid tumors and compounds of several organ systems.

The combination of Davidson et al. and Peeters et al. does not teach that the modified kringle 5 peptide will have a greater half life in vivo. Nor does the combination teach that the blood protein is human serum albumin.

Yeh et al. teach the design of a human serum albumin-CD4 conjugate (abstract). Specifically, the reference teaches that human serum albumin (HSA) represents an optimal carrier for therapeutic peptides/proteins because of its remarkably long half-life, wide *in vivo* distribution and lack of enzymatic or immunological functions (abstract). Moreover, Yeh *et al.* disclose that the elimination half-life of the HSA-CD4 conjugate was 140 fold higher than that of the soluble "unconjugated" CD4 (abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use human serum albumin instead of bovine serum albumin as the carrier protein in view of the teachings of Yeh *et al.*. One would have been motivated to do so because as taught by Yeh *et al.*, human serum albumin (HSA) represents an optimal carrier for therapeutic peptides/proteins because of its remarkably long half-life, wide *in vivo* distribution and lack of enzymatic or immunological functions. Further, as taught by Yeh *et al.*, the elimination half-life of the conjugate was increased as compared to the "unconjugated" antibody. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by using human serum albumin

as the carrier protein as taught by Yeh *et al.*, one would achieve a peptide conjugate which has greater half-life in vivo as compared to the unconjugated peptide.

Note: While Davidson et al. teaches a peptide and a method of using the patentably disclosed amino acid sequence represented by SEQ ID NO: 39, the reference does not teach or suggest administering the amino acid sequence with the addition of a MPA group. As such, claim 33 appears to be free of the prior art and allowable.

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brandon J Fetterolf, PhD
Examiner
Art Unit 1642

BF

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER
11/14/05